THE U.S. DEPARTMENT OF DEFENSE
PHARMACOECONOMIC CENTER

UPDATE

June 18, 1999
Volume 99, Issue 7
Published Monthly
Back Issues on the PEC Website at www.pec.ha.osd.mil

Restructuring the National Mail Order Pharmacy Formulary

In This Issue

Coming Next Issue

Summary of the DoD/VA

Tobacco Use Cessation

Clinical Practice Guideline

HIGHLIGHTS OF THE DOD PHARMACY & THERAPEUTICS COMMITTEE MEETING, MAY 14, 1999

The first order of business at the May meeting of the DoD Pharmacy & Therapeutics (P&T) Committee was the approval of a Pharmacoeconomic Center proposal to restructure the National Mail Order Pharmacy (NMOP) formulary. The purpose of the restructuring was to:

- Enable patients and providers to more easily and accurately determine the availability of medications in the NMOP Program.
- Increase the use of medications that offer significant clinical or economic advantages compared to other medications.
- Support compliance with DoD and VA/DoD pharmaceutical contracts

The NMOP Preferred Drug List (PDL) is replaced by an NMOP formulary that includes all non-injectable prescription drugs that are not excluded from the formulary due to TRICARE policy or DoD P&T Committee decision, as well as selected injectable drugs that are intended for self-administration or are commonly administered in the home setting. A limited number of over-the-counter drugs and products will also be dispensed through the NMOP.

Drugs may be designated by the DoD P&T Committee as subject to prescribing guidelines or prior authorization criteria that must be met before the drug is dispensed. Some drugs may be subject to quantity restrictions. In addition, non-preferred drugs and their preferred alternatives will be designated based on efficacy, safety, and/or cost. When a patient submits a prescription for a non-preferred drug, the prescriber will be contacted to request a change to a preferred alternative drug. If the prescriber agrees that a preferred alternative drug is clinically appropriate, the prescription will be changed. If the prescriber does not agree to the change, the prescription will be dispensed as written.

Drugs newly approved by the Food & Drug Administration (FDA) that are pending P&T Committee review will not be available through the NMOP until the P&T Committee completes the review and assigns the drug to the appropriate section on the NMOP formulary.

Please see the tables on Pages 2-3 for more NMOP formulary details.

The Department of Defense
National Mail Order Pharmacy Formulary

Current as of 8 June 99

Establishing the Non-Preferred Drugs/Preferred Alternatives List

- The PEC reviewed 342 drugs that were "mapped" to drugs on the former NMOP Preferred Drug List (PDL).*
- Based on comparative safety, efficacy, and cost; utilization in the NMOP; and the rate at which prescribers were willing to switch to a preferred agent, the PEC recommended to the DoD P&T Committee that only 8 of the 342 drugs should continue to be categorized as non-preferred. Eleven additional drugs with more cost-effective alternatives were identified through analysis of the top 200 drugs (by cost) in the NMOP for calendar year 1998.
- Acting on recommendations made by the PEC, the DoD P&T Committee selected the non-preferred drugs and preferred alternatives for the initial version of the revised NMOP formulary. This list will be periodically updated. Drugs may be added or dropped based on utilization of the drug or drug class in the NMOP; comparative safety, efficacy, and cost; and the rate at which prescribers are willing to switch to a preferred agent. A limiting factor to the growth of the list are the costs (including time and inconvenience to patients and prescribers) associated with communicating with prescribers to request switches.
- By focusing on high-volume drugs with acceptable and more cost-effective alternatives, it was possible to decrease the previous list of 342 drugs to fewer than 15 selected agents, while *decreasing* projected costs by approximately $700,000 annually. In addition, this change is expected to reduce the number of telephone calls that are made by Merck Medco to request changes in therapy by about 8000 calls per year. (Estimates based on CY98 NMOP usage data.)

* When a prescription for a "mapped" drug was received, a Merck-Medco pharmacist called the prescriber to request a change to an agent on the PDL. For the revised NMOP formulary, drugs previously identified as 'mapped drugs' will now be referred to as non-preferred drugs; alternate drugs will be referred to as "preferred alternatives" or "preferred drugs."

Section I: Covered Drugs

A. All non-injectable prescription drugs (unless listed as excluded in Section II), subject to the following limitations:

1. Non-Preferred Drugs & Preferred Alternatives

Non-Preferred	Preferred
Astemizole (Hismanal)	➢ **Cetirizine (Zyrtec)** **Fexofenadine (Allegra)** **Loratadine (Claritin)**
Diclofenac extended release (ER) (Voltaren XR)	➢ **Diclofenac (generic)** **Naproxen (generic)** **Ibuprofen (generic)** **Salsalate (generic)** **Piroxicam (generic)**
Diltiazem ER (Cardizem CD) Diltiazem ER (Dilacor XR) Diltiazem ER (Diltia XT)	➢ **Diltiazem ER (Tiazac)**
Etodolac ER (Lodine XL)	➢ **Etodolac (generic)** **Ibuprofen (generic)** **Naproxen (generic)** **Sulindac (generic)** **Piroxicam (generic)**
Famciclovir (Famvir)	➢ **Acyclovir (generic)**
Nabumetone (Relafen)	➢ **Salsalate (generic)** **Naproxen (generic)** **Ibuprofen (generic)** **Sulindac (generic)** **Piroxicam (generic)**
Naproxen sodium ER (Naprelan)	➢ **Naproxen (generic)** **Ibuprofen (generic)** **Salsalate (generic)** **Sulindac (generic)** **Piroxicam (generic)**
Nifedipine ER (Procardia XL)	➢ **Nifedipine ER (Adalat CC)**
Oxaprozin (Daypro)	➢ **Salsalate (generic)** **Naproxen (generic)** **Ibuprofen (generic)** **Sulindac (generic)** **Piroxicam (generic)**
Oxybutynin ER (Ditropan XL)	➢ **Oxybutynin (generic)**
Tolterodine (Detrol)	➢ **Oxybutynin (generic)**
Valacyclovir (Valtrex)	➢ **Acyclovir (generic)**
Zileuton (Zyflo)	➢ **Montelukast (Singulair)** **Zafirlukast (Accolate)**

DoD NMOP Formulary (Continued)
Current as of 8 June 99

Section I: Covered Drugs

2. Drugs Subject to Practice Guidelines / Prior Authorization

- Sildenafil (Viagra)
- Celecoxib (Celebrex)*
- Etanercept (Enbrel)*

Will not be available until Defense Supply Center Philadelphia (DSCP) and Merck-Medco establish procedures for implementing prescribing guidelines

B. Covered Injectable Drugs*

- Alprostadil intracavernosal injection (Caverject)
- Antihemophilic Factor VIII
- Antihemophilic Factor IX Complex
- Calcitonin salmon injection
- Cyanocobalamin injection
- Epoetin alfa, recombinant (Epogen, Procrit)
- Filgrastim (Neupogen) injection
- Glatiramer acetate (Copaxone) injection
- Glucagon
- Goserelin acetate (Zoladex) implant syringe
- Insect Sting Treatment Kit
- Insulin
- Insulin analog (Humalog) injection
- Interferon Alpha (Infergen, Roferon-A, Intron A, Rebetron)
- Interferon Beta (Avonex, Betaseron)
- Interferon Gamma-1b (Actimmune)
- Leuprolide (Lupron) depot and subcutaneous injections
- Menotropins (Repronex) injection
- Octreotide (Sandostatin) subcutaneous injection
- Sargramostim (Leukine) injection
- Somatrem (Protropin)
- Somatropin (Humatrope)
- Sumatriptan (Imitrex) injection
- Urofollitropin (Fertinex) injection

**** many of these agents currently have quantity restrictions***

C. Covered OTC Products

- Alcohol swabs, needles and syringes (for injectable drugs dispensed for home injection only)*
- Glucose test strips
- Insulin and insulin syringes
- Lancets*
- Niacin (for antilipemic therapy)

Will not be available until DSCP and Merck-Medco establish procedures for supplying these items.

Section II: Excluded Drugs

A. Drug Classes Excluded for <u>Active Duty Members Only</u>:

- Amphetamines
- CNS stimulants
- Controlled substances in Schedules II, III, IV, V

B. Excluded Drug Classes:

- Anabolic steroids
- Contraceptive creams, foams, implants, injections, jellies
- Immune globulins
- Immunizations
- Injectable drugs (unless listed in the Covered Injectable Drugs section)
- Legend prenatal vitamins for males, and females age 46 and over
- Legend vitamins (except Vitamin D, Vitamin K, Folic Acid, and Vitamin B-12 injection)
- Over-the-counter (OTC) drugs (unless listed in the Covered OTC Products Section)
- Smoking deterrents
- Vaccines

C. Exclusions by Drug Use:

- Drugs for cosmetic use as a result of the aging process (e.g., tretinoin cream (Renova)) or whose sole use is to stimulate hair growth [e.g., topical minoxidil (Rogaine), finasteride (Propecia)].
- Drugs for investigational use
- Drugs for obesity and/or weight reduction

D. Specific Drug Exclusions:

- Clozapine (Clozaril)
- Quinine
- Thalidomide (ThaAlomid)
- Tretinoin (Retin-A) age 36 and over

Section III: Drugs Pending DoD P&T Committee Review

- Cilostazol (Pletal)
- Rofecoxib (Vioxx)
- Rosiglitazone (Avandia)

FURTHER HIGHLIGHTS OF THE MAY 14, 1999 DOD PHARMACY & THERAPEUTICS COMMITTEE MEETING

Changes to the Basic Core Formulary

- Beclomethasone (Vancenase pockethaler) was removed from the BCF. The BCF will specify that MTFs must continue to carry a nasal corticosteroid on their formularies, but facilities may select the specific agent or agents. The committee intends to review the corticosteroid nasal inhalers at the next meeting to see if a specific inhaler should be selected for the BCF in order to standardize availability across the Military Health System.

- The BCF listing for conjugated estrogen vaginal cream (Premarin) was changed to specify an "estrogenic vaginal cream." All MTFs must carry an estrogenic vaginal cream on their formularies but may select the specific product. This item arose from an MTF request to allow the use of estropipate vaginal cream (Ogen) rather than Premarin, as there are no apparent differences in efficacy or safety between the two products and the current DAPA price for Premarin vaginal cream is almost twice that of Ogen vaginal cream.

Drugs discussed at the 14 May 99 meeting of the DoD P&T Committee included:

- Celecoxib
- Etanercept
- Sevelamer HCl
- Modafinil
- Polyethylene glycol 3350
- Niacin

None of the above drugs were added to the BCF.

Celecoxib (Celebrex; Searle/ Pfizer), a selective COX-2 inhibitor, is significantly more expensive than other non-steroidal anti-inflammatory drugs (NSAIDs) but may cause fewer serious gastrointestinal adverse events. Celecoxib will be available through the NMOP, subject to a prescribing guideline designed to target its use to patients who are at high risk for gastrointestinal adverse events, as soon as procedures for implementing the prescribing guideline/prior authorization have been established.

Etanercept (Enbrel; Immunex/ Wyeth-Ayerst) is a recombinant tumor necrosis factor receptor product for the treatment of moderate to severe rheumatoid arthritis in patients who have failed other agents. The cost of twice-weekly subcutaneous injections with etanercept at the current DAPA price is approximately $655 per month.

The committee decided to make etanercept available through the NMOP under a prescribing guideline targeting use of the drug to patients who have failed previous disease-modifying antirheumatic drug therapy. The guideline will also address the apparent increased risk of serious infections in patients receiving etanercept recently detected through post-marketing surveillance. Etanercept will be available through the NMOP as soon as procedures for implementing the prescribing guideline/prior authorization have been established. In order to limit potential waste, the NMOP will dispense no more than a 30-day supply of etanercept (2 cartons of 4 injections) at a time.

Sevelamer hydrochloride (Renagel; GelTex/Genzyme), a nonabsorbable hydrogel polymer, is indicated for the reduction of serum phosphorus in patients with end-stage renal disease on renal dialysis. Use of sevelamer as a phosphate binder avoids the problems associated with hypercalcemia or aluminum toxicity resulting from calcium- or aluminum-containing products. Sevelamer was added to the NMOP formulary.

Modafinil (Provigil; Cephalon), a non-amphetamine central nervous system stimulant, is indicated to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy. Modafinil is a C-IV scheduled drug, unlike the C-II stimulants commonly used in narcoleptic patients. The committee expressed concern about the potential for inappropriate use of modafinil to increase alertness among patients who do not have narcolepsy. Modafinil was added to the NMOP formulary; usage patterns will be monitored for evidence of inappropriate use.

Polyethylene glycol 3350, NF powder (MiraLax; Braintree), an osmotic laxative indicated for the relief of occasional constipation, was added to the NMOP formulary.

Niacin for antilipemic therapy: The committee reaffirmed its position that the NMOP should provide niacin (in both OTC and prescription forms)

for antilipemic therapy. The committee does not intend that niacin should be provided for vitamin supplementation. The restructured NMOP formulary automatically includes prescription forms of niacin. *The committee decided to add over-the-counter (OTC) forms of niacin prescribed for antilipemic therapy to the list of OTC items that are covered by the NMOP. The implementation of this decision is contingent on TMA West policy review.*

Corticosteroid Oral Inhalers: The committee also discussed corticosteroid oral inhalers at the 14 May 99 meeting. There have been several recent DAPA price increases for agents in this class, including triamcinolone (Azmacort) and beclomethasone (Vanceril, Vanceril-DS). The cost per day for triamcinolone and beclomethasone inhalers remains less than the cost per day for most other corticosteroids for oral inhalation. *The committee decided to make no changes to the corticosteroid oral inhalers on the BCF at the present time, but will continue to monitor price changes in this drug class.*

Other Issues

Fertility Drugs: There are considerable inconsistencies between coverage of fertility agents by managed care support contractors and the NMOP. The TRICARE policy manual classifies noncoital reproductive technologies (e.g., artificial insemination, in vitro fertilization, gamete intrafallopian transfer) as non-covered treatments and specifies that services and supplies directly related to a non-covered procedure are not covered. Based on this policy, managed care support contractors in some TRICARE regions utilize prior authorization procedures to deny coverage at retail network pharmacies for fertility drugs when they are prescribed for use with noncoital reproductive technologies. Because the NMOP does not currently have similar prior authorization criteria, in some cases patients who were previously denied coverage through a retail network pharmacy were able to subsequently obtain the drugs from the NMOP.

The committee concluded that this issue was too complex to be solved at the meeting. A subcommittee was appointed to investigate the issue in greater detail, obtain input from fertility experts and others outside of the P&T Committee, and recommend actions to make the coverage of fertility drugs consistent in the NMOP and the retail pharmacy networks.

Provision of needles, syringes, alcohol pads, and lancets through the NMOP: *The committee decided that the NMOP should supply needles, syringes, and alcohol pads when a medication is dispensed for home injection. The NMOP should also supply alcohol pads and lancets for diabetic patients.* However, the committee acknowledged the possibility that when co-pays and dispensing fees were taken into account, providing these items might substantially increase costs to the government and provide little if any benefit to beneficiaries. *The provision of these items through the NMOP will be contingent upon the ability of the NMOP Contracting Officer Technical Representative (COTR) and the contracting officer to identify methods by which these items can be provided at a reasonable cost.*

Contracting Initiative for Blood Glucose Test Strips: The PEC recommended discontinuation of the current contracting initiative to select a single blood glucose test strip for a closed class on the BCF for the following reasons: 1) a contract for blood glucose test strips would be likely to take 8 to 12 months to complete, given the number of contracting initiatives currently in progress, and 2) some MTFs are reluctant to switch patients to the test strip that is currently on the BCF (Precision QID) because they do not want to switch patients twice in the event that a contract is awarded for a different test strip. The committee agreed that it is unreasonable to hold up MTF formulary decisions for that length of time. *The committee decided to discontinue the current blood glucose test strip contracting initiative. Precision QID remains as the only blood glucose test strip on the BCF.*

NMOP Quantity Limits: *A review of quantity limits for migraine agents, ophthalmics, and topical agents in the NMOP* was referred to a subcomittee that will develop recommendations to be reviewed at the next meeting.

Further Information: Please refer to the full text of the minutes posted on the PEC website (www.pec.ha.osd..mil) for further details. The next meeting of the DoD P&T Committee will be held on 13 August 1999 at Fort Sam Houston, Texas. MTFs are requested to submit agenda items to the PEC by 16 July 1999.

The restructured DoD NMOP Formulary is posted on the PEC website:

www.pec.ha.osd.mil/nmop/nmophome.htm.

Summary of efficacy, safety and cost issues associated with the selective COX-2 inhibitor, celecoxib (Celebrex)

- Celecoxib (Celebrex; Searle/Pfizer) does not appear to be any more or any less effective than other non-steroidal anti-inflammatory drugs (NSAIDs) in treating the symptoms of osteoarthritis (OA) or rheumatoid arthritis (RA).
- The potential benefit of a cyclooxygenase-2 (COX-2) inhibitor such as celecoxib is primarily due to the lack of inhibition of cyclooxygenase-1 (COX-1) at therapeutic doses. Lack of COX-1 inhibition is mechanistically related to a potential decrease in the risk of GI adverse events (ulceration, bleeding, and perforation). Celecoxib lacks the platelet effects associated with other NSAIDs. Celecoxib does not appear to differ from other NSAIDs in terms of renal adverse effects or use during pregnancy.
- Labeling for celecoxib includes the same warnings about increased risk of adverse gastrointestinal (GI) events as other NSAIDs. During its first three months on the market, 10 deaths and 11 serious gastrointestinal events (bleeding or ulcer) were reported in patients receiving celecoxib. This must be considered in the context of the number of patients who have been exposed to celecoxib during this period, as well as the expected background rate of adverse GI events in patients not exposed to NSAIDs.
- Trials with celecoxib have shown a significant reduction in the incidence of endoscopically detected ulcerations compared to other NSAIDs. The correlation between endoscopic ulcers and actual GI adverse events is unclear. Premarketing trials with celecoxib were not designed to collect outcomes data on actual events, and no firm conclusions can be drawn from these results.
- Overall, about 10% of patients (20.7 million) in the U.S. have OA; about 1% (2.1 million) have RA. Patients with RA are typically at greater risk for NSAID-induced adverse events because they receive higher NSAID doses and are more likely to be receiving other medications that increase risk.
- For patients with rheumatoid arthritis (RA), the annual rate of GI hospitalizations is about 1.46% in patients taking NSAIDs compared to 0.27% in patients not taking NSAIDs. Number-needed-to-harm (NNH) = 84. For patients with osteoarthritis (OA), the annual rate of GI hospitalizations is about 0.73% in patients taking NSAIDs compared to 0.29% in patients not taking NSAIDs. NNH = 227.
- *If the assumption is made that the rate of GI adverse events in patients receiving celecoxib is equal to the rate in patients not receiving NSAIDs,* 84 RA patients or 227 OA patients (or an even greater number of patients in the general patient population) would have to be treated with celecoxib (rather than NSAIDs) for 1 year in order to avert 1 GI hospitalization. Treating 84 RA patients with celecoxib would increase annual drug costs by approximately $41,403 compared to

Estimated drug costs in the NMOP Program associated with celecoxib compared to conventional NSAIDs, *assuming risk of NSAID-induced GI events with celecoxib equals background rate*

Patient Population	**Number-needed-to-treat** This many patients must be treated with celecoxib...	...to avert one of these events that would otherwise have occurred with conventional NSAIDs...	Incremental drug cost if celecoxib is used in place of conventional NSAIDs ((NNT x cost per year for celecoxib) - (NNT x cost of conventional NSAIDs)*
RA patients	84	GI hospitalization	$41,403
RA patients	2647	death d/t GI complications	$1,304,706
OA patients	227	GI hospitalization	$111,888

*Assumes that the daily cost of celecoxib is $2.06 for all patients ($751.90 year) and that the daily cost of treatment with other NSAIDs is $0.71 ($259 year), based on CY98 estimates for total number of days supply of NSAIDs supplied through the NMOP and the total mean daily cost for NSAID therapy. Facilities with a lower mean daily cost for NSAIDs would experience greater increases in drug costs if patients were switched from current NSAID therapy to celecoxib.

Summary of efficacy, safety and cost issues associated with celecoxib (continued)

treatment with conventional NSAIDs. Treating 227 OA patients with celecoxib would increase annual drug costs by approximately $111,888 compared to treatment with conventional NSAIDs. (See table on facing page)

Please note that these estimates are based on the mean daily cost for NSAIDs in the National Mail Order Pharmacy (NMOP) program during calendar year 1998 (about $0.71) and an estimated mean daily cost for celecoxib of $2.06. (The estimated mean daily cost for celecoxib is based on available information regarding the dose distribution of celecoxib in actual practice. Current DAPA prices for celecoxib are $0.88 for the 100 mg capsule; $1.49 for the 200 mg capsule.) Facilities with a lower mean daily cost for NSAIDs would experience greater increases in drug costs if patients were switched from current NSAID therapy to celecoxib.

- Use of COX-2 inhibitors such as celecoxib may decrease costs by reducing the number of patients who require concomitant treatment with misoprostol, H2 blockers, or proton pump inhibitors (PPIs). However, it is difficult to quantify the number of patients who could successfully be taken off H2 blockers or PPIs, since patients may require treatment with such agents for conditions that are independent of NSAID use.
- Risk factors for increased risk of NSAID-induced GI adverse events include previous history of GI complications, age, concomitant use of corticosteroids and anticoagulants, high doses of NSAIDs, and general health status.
- A prescribing guideline designed to target the use of celecoxib to patients at high risk for a GI adverse event would minimize the number of patients who must be treated to avert such an event and maximize the *potential* safety benefit associated with celecoxib. It must be noted that an actual reduction in the rate of GI adverse events with celecoxib has not yet been demonstrated in clinical trials.

New Drug Watch

In this issue

A second "glitazone" oral antidiabetic agent

Rosiglitazone (Avandia; SmithKline Beecham) was approved on 25 May 99 for the treatment of Type 2 diabetes, both as monotherapy and in combination with metformin (Glucophage; Bristol-Myers Squibb). Studies in animal models indicate that the thiazolidinedione antidiabetic agents, including rosiglitazone and troglitazone (Rezulin; Parke-Davis), improve insulin sensitivity in muscle and adipose tissue and inhibit hepatic gluconeogenesis.

In clinical trials, rosiglitazone improved glycemic control (measured by fasting plasma glucose and hemoglobin A1c) and reduced insulin and C-peptide levels. The improvement in glycemic control was maintained during trials of up to 1 year. Addition of rosiglitazone to metformin resulted in an apparent synergistic effect on glycemic control.

The currently marketed thiazolidinedione antidiabetic agent, troglitazone (Rezulin; Warner-Lambert) has been linked to a number of cases of acute liver failure, some of which have resulted in deaths or liver transplantation. Labeling for troglitazone currently recommends that hepatic enzymes should be monitored at baseline, monthly during the first eight months of therapy, every two months for the remainder of the first year, and periodically thereafter.

No evidence of drug-induced hepatotoxicity or elevation of hepatic enzymes with rosiglitazone was noted during approximately 3600 patient-years of exposure to rosiglitazone during clinical trials. The percentage of patients experiencing elevations in ALT that exceeded three times the upper limit of normal was 0.2% in

NEW DRUG WATCH *continued from Page 7*

both rosiglitazone and placebo groups and 0.5% for active comparators.

Labeling for rosiglitazone recommends that periodic monitoring of hepatic enzymes be performed until the results of large, long-term controlled trials and post-market safety data are available. Monitoring of hepatic enzymes is recommended at baseline and every two months for the first year, and periodically thereafter. Caution is advised in patients with mildly elevated hepatic enzymes (ALT one to 2.5 times the upper limit of normal). Rosiglitazone should be discontinued in patients with persistent ALT elevations that exceed three times the upper limit of normal. Rosiglitazone does not appear to inhibit the major cytochrome P450 enzymes at therapeutic concentrations. It is extensively metabolized, predominantly by CYP2C8 and to a lesser extent by CYP2C9. No unchanged drug is excreted in the urine and circulating metabolites are considerably less potent than the parent drug. No dosage adjustment is required in patients with renal failure. Rosiglitazone should not be initiated in patients with evidence of active liver disease or increased ALT levels (exceeding three times the upper limit of normal) at baseline.

Other precautions include the possibility of resumption of ovulation in premenopausal, anovulatory women with insulin resistance; mild to moderate edema related to an increase in median plasma volume; and sustained decreases in hemoglobin and hematocrit (≤1 gm/dL and ≤3.3%, respectively).

Caution is recommended in patients with edema. Package labeling for rosiglitazone refers to two ongoing echocardiography studies of 26 to 52 weeks duration involving patients with Type 2 diabetes patients, which showed no deleterious effect on cardiac structure or function. Patients with New York Heart Association Class 3 and 4 cardiac status were not studied during clinical trials. Rosiglitazone is not indicated in these patients unless the expected benefit clearly outweighs the potential risk.

Rosiglitazone does not appear to have clinically relevant drug interactions with nifedipine, oral contraceptives, glyburide, metformin, acarbose, digoxin, warfarin, ranitidine, or a moderate amount of ethanol. Rosiglitazone is Pregnancy Category C and should not be administered while breast-feeding.

The recommended starting dose for rosiglitazone, either as monotherapy or in combination with metformin, is 4 mg once daily or 2 mg twice daily. For patients with an inadequate response after 12 weeks of treatment, the dose may be increased to 8 mg once daily or 4 mg twice daily. During clinical trials, 4 mg twice daily resulted in the greatest reduction in fasting plasma glucose and HbA1c. Rosiglitazone (Avandia) can be taken without regard to meals.

A twice daily protease inhibitor for HIV...

Agenerase (amprenavir; Glaxo Wellcome) was granted accelerated approval by the FDA on 15 April 99 for use in combination with other antiretrovirals for the treatment of HIV infection. Amprenavir may be taken twice daily, compared to three times daily for other protease inhibitors, but the capsule formulation of amprenavir requires patients to swallow eight 150-mg capsules at each dose. Amprenavir capsules and oral solution are not interchangeable on a milligram to milligram basis, since amprenavir is approximately 14% less bioavailable from the liquid formulation than from the capsules.

The efficacy of amprenavir for increasing CD4 cell counts and reducing viral load was demonstrated during a 24-week study involving 700 patients. Evidence as to the long-term benefit of amprenavir is not yet available. The most frequently reported adverse events were nausea, diarrhea, vomiting, rash and perioral paresthesia. Severe and life-threatening skin reactions, including Stevens-Johnson syndrome, occurred in 1 percent of patients during amprenavir clinical trials. Like other protease inhibitors, amprenavir may be associated with acute hemolytic anemia, diabetes mellitus, and hyperglycemia.

Amprenavir inhibits CYP3A4. Concurrent administration of amprenavir is contraindicated with astemizole, bepridil, cisapride, dihydroergotamine, ergotamine, midazolam, and triazolam. Concentration monitoring of the following drugs is recommended if amprenavir is given concurrently: amiodarone, lidocaine, tricyclic antidepressants, and quinidine. Particular caution is recommended if sildenafil is prescribed for patients receiving amprenavir, since sildenafil concentrations may increase substantially, potentially increasing adverse effects. Amprenavir is a sulfonamide with unknown cross-reactivity to drugs in the sulfonamide class.

New ARB/HCTZ combo...

A combination of irbesartan and hydrochlorothiazide (Avalide; Bristol-Myers Squibb/Sanofi) is now available for the treatment of high blood pressure.